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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/991,480 | 11/09/2001 | Jean Toma | CIBT-P06-120 | 4573 |

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| EXAMINER | |
|---|---|
| GAMETT, DANIEL C | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1647 | |

DATE MAILED: 10/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/991,480 | TOMA ET AL. | |
| | Examiner | Art Unit | |
| | Daniel C Gamett | 1647 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *17 June 2004 and 13 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-84* is/are pending in the application.

4a) Of the above claim(s) *1-29,39--63* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30-84* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *4/29/02* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/4/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Marked up copy of claims*.

## DETAILED ACTION

### *Election/Restriction*

1. Applicant's election without traverse of claims 30-38 and 40-45 in the reply filed on 17 June, 2004 is acknowledged. Claims 1-29,39, and, 46-63 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected claims, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 17 June, 2004.

### *Status of Application, Amendments and/or Claims*

2. The amendment of 13 September 2004 has been entered in full. Claims 1-29 and 39-63 are cancelled, claims 30 and 35 are amended, and new claims 64,65 and 67-85 have been added. No claim 66 was included in the amendment. Therefore, new claims 67-85 were renumbered as 66-84 by the Examiner under 37 C.F.R. 1.126. claim dependencies were also corrected.

### *Claim objections*

3. Claim 34 is objected to because of the following informality: an apparent typographical error omitting the word 'of' between 'result' and 'bacterial'.

### *Claim Rejections- U.S.C. 112*

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 30-38, 64-84 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not

described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claim 30 and 69 are drawn to a method of treating a patient with cell damage or disease comprising transplanting stem cells. The specification discloses examples in which cells transplanted into intact animals survived and expressed markers indicative of differentiation. Yet these examples do not teach "treatment" as there was no indication that the recipients of the transplanted cells derived any benefit or amelioration of symptoms. Furthermore, claim 30 is a method claim that recites one step (cell transplantation) but does not recite steps that would fully enable one knowledgeable in the art to practice the invention; for example how is the problem of rejection to be addressed? Using only autologous transplantation? Or fully histocompatible donor/recipient pairs?

6. Furthermore, Claims 34 and 77 are drawn to a method wherein transplanted cells are used to treat a patient in which cell damage or disease is the result of bacterial or viral infection. The use of cell replacement to treat the damage caused by microbial disease is not well known in the art. The applicability of the claimed invention in this context would be unpredictable, requiring extensive experimentation in view of the diversity of pathogens encompassed by the term "bacterial or viral", the myriad mechanisms by which these organisms cause cell damage or disease, the variety of bodily locations and tissues that might be damaged, and the varying extents of damage one might encounter. The requisite first step of ridding the body of the infectious agent so that the transplanted cells would not become infected would be problematic in many cases. The disclosure provides neither direction nor a working example as to how to use the claimed cellular composition in this type of treatment.

7. Claims 37 and 79 are drawn to a method wherein cells are delivered to a site of cell damage via the bloodstream. This mode of delivery is asserted in the specification, but that assertion is not accompanied by a reference that teaches successful use of this method, nor does the specification disclose how one skilled in the art would successfully employ this mode of delivery without undue experimentation. *A priori*, one would expect this method to work only in cases where the site of cell damage is in direct contact with the bloodstream. A large quantity of experimentation would be required to determine how to cause a cell deposited in the bloodstream to migrate to the site of cell damage. The specification lacks guidance or working examples regarding how to achieve this migration.
8. To summarize this section: In view of the unpredictability and complexity of cell therapy, the large amount of experimentation that would be required, the lack of guidance and working examples in the specification as discussed in paragraph 5, above, for claim 30 and 69 and their dependents, and in paragraphs 6 and 7, above, particularly for claims 34, 77, 37, and 79, the breadth of the claims, undue experimentation would be required for the skilled artisan to make and/or use the invention in claims 30-38, 64-84 in its full scope.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claim 32, 75,78,79, and 81-83 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "genetically related" in claim 32 is a relative term which renders the claim indefinite. The term "genetically related" is not defined by the

claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. "Genetically related" might mean 1st, 2nd, or 3rd degree relatives, sharing the same blood type, or sharing 2,3, 4, or more major histocompatibility antigens. Indeed, all humans are genetically related in that they appear to have descended from a common ancestor and their DNA sequences are more similar one to another as compared to DNA sequences from other species.

11. Claims 75, 78, 79, 81, 82, and 83 recite the limitation "said multipotent cells" and Claim 81 further recites the limitations "said population" in "the method of claim 69". There is insufficient antecedent basis for these limitations in these claims. Although cell populations and multipotent cells are implied in claim 69, those terms are not actually used.

***Claim rejections- U.S.C. 102***

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

13. Claims 30-38, 65, 66-80, and 82-84 are rejected under 35 U.S.C. 102(e) as being anticipated by Weiss *et al.*, U.S. Patent 5851822, (filed 06/07/1995; issued 12/22/1998). Claims 30, 69, and claims dependent therefrom are drawn to methods of treating a patient with cell damage or disease comprising transplanting to said patient a population of multipotent mammalian cells, said multipotent mammalian cells form non-adherent clusters in culture, are self-renewing, are positive for nestin and fibronectin protein, and differentiate into both neuronal and non-neuronal cells. It is recognized that the specification discloses cells that arguably represent a population of stem cells that are distinct from those previously described by Weiss *et al.* or by others. However, the neural stem cells disclosed in Weiss *et al.* meet the limitations recited in claims 30 and 69. The neural stem cells disclosed in Weiss *et al.* are multipotent mammalian cells that proliferate, self-renew, and which can be induced to differentiate into neuronal and non-neuronal cell types (see fig. 2 of Weiss et al.). The neural stem cells disclosed in Weiss *et al.* form non-adherent clusters in culture (see fig. 1 of Weiss *et al.*) and they are positive for nestin (column 17, lines 18-33). Weiss *et al.* do not state that their cells are positive for fibronectin. However this is an inherent property of the cells disclosed by Weiss *et al.* Indeed, the instant specification indicates that fibronectin expression is not a feature that distinguishes the stem cells described therein from other stem cells in that it discloses that both mesenchymal stem cells and the skin-derived multipotent stem cells of the invention express fibronectin (figure 22 and p. 41 line 29). In the absence of evidence to the contrary, it may be reasonably expected that the cells disclosed in Weiss *et al.* also comprised cells that express fibronectin. Finally, the neural stem cells disclosed by Weiss *et al*, could be isolated from the ependyma (see Example 5 in column 35), which is an

epithelial layer. Thus the cells disclosed by Weiss et al., meet the limitation of claim 69 (a) which recites "culturing a dissociated sample of epithelial tissue".

14. In addition to their dependency from rejected claim 30 or 69, the further limitations recited in claims 33, 35, 36, 38, 39, 65, 73, 76, 78, 81 and 82 are specifically anticipated in Weiss *et al.* For example, Weiss *et al.* column 42 lines 31-60, teaches the use of neural stem cells (as in claims 30 and 69) to treat a human patient (as in claims 38 and 80) with a neurodegenerative disease (as in claims 33 and 76) by delivering stem cells to a site of degeneration in the brain (as in claims 36 and 78). Column 64, lines 38-49 teach an animal model in which spasticity induced by transaction of the spinal chord (a traumatic injury as in claims 35 and 73) is treated by transplantation of neural stem cells. Proliferation in the absence of EGF, recited in claims 65 and 82, is disclosed in Weiss *et al.* column 16, lines 46-55, which indicate that EGF is but one of many trophic factors that may be used for inducing proliferation.

***Conclusion***

A point of interest concerning expression of fibronectin by neural stem cells and fibronectin: It is likely that Weiss *et al*, did not recite expression of fibronectin simply because they did not look for it. Subsequently it has been shown that neural stem cells in neurospheres do express fibronectin (Campos et al. (2004) Development 131(14):3433-44).

No claims are allowed.

***Advisory Information***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel C Gamett, Ph.D. whose telephone number is 571 272 1853. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571 272 0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

dcg

Elizabeth C. Kemmerer